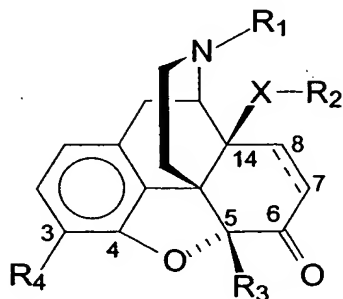
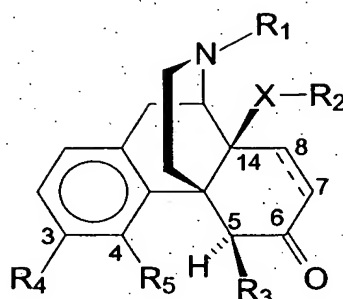


Claims

- Compounds of the formula (I) or (Ia),



(I)



(Ia)

in which the substituents have the following significance:

R₁: C₁-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkinyl; C₃-C₁₆-(cyclical saturated group)alkyl, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyl, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyl, where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyl, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl;

R₂: subject to the following definition of X, hydrogen, C₄-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkinyl; C₃-C₁₆-(cyclical saturated group)alkyl, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyl, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyl, where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyl, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl; C₃-C₆-alkenoyl; C₃-C₆-alkinoyl; C₉-C₁₆-arylalkenoyl, where aryl is C₆-C₁₀-aryl and alkenoyl is C₃-C₆-alkenoyl; C₉-C₁₆-arylalkinoyl, where aryl is C₆-C₁₀-aryl and alkynoyl is C₃-C₆-alkinoyl;

R₃: hydrogen; C₁-C₆-alkyl; C₂-C₆-alkenyl; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; alkoxyalkyl, where alkoxy is C₁-C₆-alkoxy and alkyl is C₁-C₆-alkyl; CO₂(C₁-C₆-alkyl); CO₂H; CH₂OH.

R₄: hydrogen; hydroxy; C₁-C₆-alkyloxy; C₂-C₁₀-alkyloxyalkoxy, where alkyloxy is C₁-C₄ and alkoxy is C₁-C₆-alkyloxy; C₂-C₆-alkenyloxy; C₂-C₆-alkinyloxy; C₃-C₁₆-(cyclical saturated group)alkyloxy, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyloxy, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical

saturated group)alkinyloxy where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyloxy, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyloxy, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyloxy, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl; C₁-C₆-alkanoyloxy; C₃-C₆-alkenoyloxy; C₃-C₆-alkinoyloxy; C₇-C₁₆-arylalkanoyloxy, where aryl is C₆-C₁₀-aryl and alkanoyloxy is C₂-C₆-alkanoyloxy; C₉-C₁₆-arylalkenoyloxy, where aryl is C₆-C₁₀-aryl and alkenoyloxy is C₃-C₆-alkenoyloxy; C₉-C₁₆-arylalkinoyloxy, where aryl is C₆-C₁₀-aryl and alkinoyloxy is C₃-C₆-alkinoyloxy;

R₅: hydrogen; hydroxy; C₁-C₆-alkyloxy; C₂-C₁₀-alkyloxyalkoxy, where alkyloxy is C₁-C₄ and alkoxy is C₁-C₆-alkyloxy; C₂-C₆-alkenyloxy; C₂-C₆-alkinyloxy; C₃-C₁₆-(cyclical saturated group)alkyloxy, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyloxy, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyloxy, where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyloxy, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyloxy, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyloxy, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl; C₂-C₆-alkanoyloxy; C₇-C₁₆-arylalkanoyloxy, where aryl is C₆-C₁₀-aryl and alkanoyloxy is C₂-C₆-alkanoyloxy;

X is oxygen, sulphur or methylene;

wherein a single or double bond can be present between the carbon atoms of numbers 7 and 8,

wherein alkyl, alkenyl and alkynyl can each be branched or unbranched, aryl can be unsubstituted or mono-, di- or trisubstituted, independently in each case, with hydroxy, halogen, nitro, cyano, thiocyanato, trifluoromethyl, C₁-C₃-alkyl, C₁-C₃-alkoxy, CO₂H, CONH₂, CO₂(C₁-C₃-alkyl), CONH(C₁-C₃-alkyl), CON(C₁-C₃-alkyl)₂, CO(C₁-C₃-alkyl); amino; (C₁-C₃-monoalkyl)amino, (C₁-C₃-dialkyl)amino; C₅-C₆-cycloalkylamino, (C₁-C₃-alkanoyl)amido, SH, SO₃H, SO₃(C₁-C₃-alkyl), SO₂(C₁-C₃-alkyl), SO(C₁-C₃-alkyl), C₁-C₃-alkylthio or C₁-C₃-alkanoylthio,

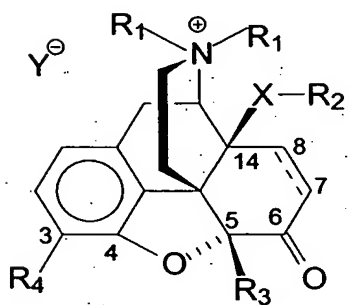
wherein -(cyclical saturated group) is either preferably C₃-C₁₀-cycloalkyl or a heterocyclical group with 2 to 9 carbon atoms, containing further one or more heteroatoms,

with the exception of compounds where R₁ is methyl, R₂ is C₄-C₆-alkyl, R₃ is hydrogen or methyl, R₄ is hydroxy or methoxy and R₅ is hydroxy, methoxy or an oxygen atom bound to the carbon atom in the 5th position, when X is oxygen;

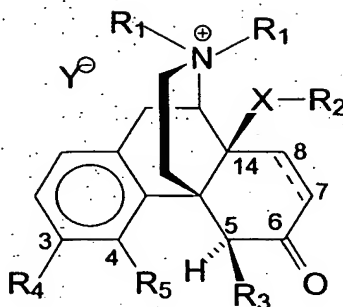
with the further exception of compounds where R₁ is cyclopropylmethyl and XR₂ is benzyloxy, when R₄ is oxygen or benzyloxy and R₅ is an oxygen atom bound to the carbon atom in the 5th position;

with the further exception of compounds where R₁ is cyclopropylmethyl and XR₂ is benzyloxy, when R₄ is oxygen, hydroxy or benzyloxy and R₅ is hydroxy or methoxy.

2. Compounds of the formula (IA) or (IAa),



(IA)



(IAa)

where the substituents have the following significance:

R_1 : C_1 - C_6 -alkyl; C_2 - C_6 -alkenyl; C_2 - C_6 -alkinyl; C_3 - C_{16} -(cyclical saturated group)alkyl, where alkyl is C_1 - C_6 ; C_4 - C_{16} -(cyclical saturated group)alkenyl, where alkenyl is C_2 - C_6 ; C_4 - C_{16} -(cyclical saturated group)alkinyl, where alkinyl is C_2 - C_6 ; C_7 - C_{16} -arylalkyl, where aryl is C_6 - C_{10} -aryl and alkyl is C_1 - C_6 -alkyl; C_8 - C_{16} -arylalkenyl, where aryl is C_6 - C_{10} -aryl and alkenyl is C_2 - C_6 -alkenyl; C_8 - C_{16} -arylalkinyl, where aryl is C_6 - C_{10} -aryl and alkinyl is C_2 - C_6 -alkinyl;

wherein the two substituents R_1 can be the same or different;

R_2 : subject to the following definition of X, hydrogen, C_1 - C_6 -alkyl; C_2 - C_6 -alkenyl; C_2 - C_6 -alkinyl; C_3 - C_{16} -(cyclical saturated group)alkyl, where alkyl is C_1 - C_6 ; C_4 - C_{16} -(cyclical saturated group)alkenyl, where alkenyl is C_2 - C_6 ; C_4 - C_{16} -(cyclical saturated group)alkinyl, where alkinyl is C_2 - C_6 ; C_7 - C_{16} -arylalkyl, where aryl is C_6 - C_{10} -aryl and alkyl is C_1 - C_6 -alkyl; C_8 - C_{16} -arylalkenyl, where aryl is C_6 - C_{10} -aryl and alkenyl is C_2 - C_6 -alkenyl; C_8 - C_{16} -arylalkinyl, where aryl is C_6 - C_{10} -aryl and alkinyl is C_2 - C_6 -alkinyl; C_2 - C_6 -alkanoyl; C_3 - C_6 -alkenoyl; C_3 - C_6 -alkinoyl; C_8 - C_{16} -arylalkanoyl, where aryl is C_6 - C_{10} -aryl and alkanoyl is C_2 - C_6 -alkyl; C_9 - C_{16} -arylalkenoyl, where aryl is C_6 - C_{10} -aryl and alkenoyl is C_3 - C_6 -alkenoyl; C_9 - C_{16} -arylalkinoyl, where aryl is C_6 - C_{10} -aryl and alkinoyl is C_3 - C_6 -alkinoyl;

R_3 : hydrogen; C_1 - C_6 -alkyl; C_2 - C_6 -alkenyl; C_7 - C_{16} -arylalkyl, where aryl is C_6 - C_{10} -aryl and alkyl is C_1 - C_6 -alkyl; C_8 - C_{16} -arylalkenyl, where aryl is C_6 - C_{10} -aryl and alkenyl is C_2 - C_6 -alkenyl; alkoxyalkyl, where alkoxy is C_1 - C_6 -alkoxy and alkyl is C_1 - C_6 -alkyl; $CO_2(C_1$ - C_6 -alkyl); CO_2H ; CH_2OH .

R_4 : hydrogen; hydroxy; C_1 - C_6 -alkyloxy; C_2 - C_{10} -alkyloxyalkoxy, where alkyloxy is C_1 - C_4 and alkoxy is C_1 - C_6 -alkyloxy; C_2 - C_6 -alkenyloxy; C_2 - C_6 -alkinyloxy; C_3 - C_{16} -(cyclical saturated group)alkyloxy, where alkyl is C_1 - C_6 ; C_4 - C_{16} -(cyclical saturated group)alkenyloxy, where alkenyl is C_2 - C_6 ; C_4 - C_{16} -(cyclical

saturated group)alkynyloxy where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyloxy, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyloxy, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkynyloxy, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl; C₂-C₆-alkanoyloxy; C₃-C₆-alkenoyloxy; C₃-C₆-alkinoyloxy; C₈-C₁₆-arylalkanoyloxy, where aryl is C₆-C₁₀-aryl and alkanoyloxy is C₂-C₆-alkanoyloxy; C₉-C₁₆-arylalkenoyloxy, where aryl is C₆-C₁₀-aryl and alkenoyloxy is C₃-C₆-alkenoyloxy; C₉-C₁₆-arylalkinoyloxy, where aryl is C₆-C₁₀-aryl and alkinoyloxy is C₃-C₆-alkinoyloxy;

R₅: hydrogen; hydroxy; C₁-C₆-alkyloxy; C₂-C₁₀-alkyloxyalkoxy, where alkyloxy is C₁-C₄ and alkoxy is C₁-C₆-alkyloxy; C₂-C₆-alkenyloxy; C₂-C₆-alkynyloxy; C₃-C₁₆-(cyclical saturated group)alkyloxy, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyloxy, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkynyloxy, where alkynyl is C₂-C₆; C₇-C₁₆-arylalkyloxy, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyloxy, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkynyloxy, where aryl is C₆-C₁₀-aryl and alkynyl is C₂-C₆-alkynyl; C₂-C₆-alkanoyloxy; C₇-C₁₆-arylalkanoyloxy, where aryl is C₆-C₁₀-aryl and alkanoyloxy is C₂-C₆-alkanoyloxy;

X is oxygen, sulphur or methylene;

Y⁻ is I⁻, Br⁻, Cl⁻, OH⁻ or another pharmacologically acceptable counterion;

wherein a single or double bond can be present between the carbon atoms of numbers 7 and 8,

wherein alkyl, alkenyl and alkynyl can each be branched or unbranched, aryl can be unsubstituted or mono-, di- or trisubstituted, independently in each case, with hydroxy, halogen, nitro, cyano, thiocyanato, trifluoromethyl, C₁-C₃-alkyl, C₁-C₃-alkoxy, CO₂H, CONH₂, CO₂(C₁-C₃-alkyl), CONH(C₁-C₃-alkyl), CON(C₁-C₃-alkyl)₂, CO(C₁-C₃-alkyl); amino; (C₁-C₃-monoalkyl)amino, (C₁-C₃-dialkyl)amino; C₅-C₆-cycloalkylamino, (C₁-C₃-alkanoyl)amido, SH, SO₃H, SO₃(C₁-C₃-alkyl), SO₂(C₁-C₃-alkyl), SO(C₁-C₃-alkyl), C₁-C₃-alkylthio or C₁-C₃-alkanoylthio,

wherein -(cyclical saturated group) is either preferably C₃-C₁₀-cycloalkyl or a heterocyclical group with 2 to 9 carbon atoms, containing furthermore one or more heteroatoms.

3. Compounds of the formulae (I) or (IA) of Claims 1 and 2, in which X is oxygen; R₁ is C₁-C₆-alkyl; C₂-C₆-alkenyl; C₄-C₁₆-cycloalkylalkyl, where cycloalkyl is C₃-C₁₀ and alkyl is C₁-C₆; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; R₂ is C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; R₃ is hydrogen or methyl; R₄ is hydroxy, methoxy or acetoxy.

4. Compounds of the formula (IA) of Claim 2, in which X is oxygen; R₁ is C₁-C₆-alkyl; C₂-C₆-alkenyl; C₄-C₁₆-cycloalkylalkyl, where cycloalkyl is C₃-C₁₀ and alkyl is C₁-C₆; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; R₂ is C₁-C₆-alkyl or C₂-C₆-alkenyl, R₃ is hydrogen or methyl; R₄ is hydroxy, methoxy or acetoxy.

5. Compounds of Claims 1 and 2, selected from:

17-allyl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-allyl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-allyl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-allyl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclobutylmethyl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclobutylmethyl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclobutylmethyl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclobutylmethyl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 4,5 α -epoxy-3-methoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, 4,5 α -epoxy-3-hydroxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, 17-propyl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-propyl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-propyl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-propyl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-tetrahydrofurfuryl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-tetrahydrofurfuryl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-tetrahydrofurfuryl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-tetrahydrofurfuryl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-(2-phenylethyl)-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-(2-phenylethyl)-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-(2-phenylethyl)-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-(2-phenylethyl)-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-ethyl-4,5 α -epoxy-3-methoxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-ethyl-4,5 α -epoxy-3-hydroxy-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-ethyl-4,5 α -epoxy-3-methoxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-ethyl-4,5 α -epoxy-3-hydroxy-5 β -methyl-14 β -(3-phenylpropyloxy)morphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-14 β -[(2-

methylbenzyl)oxy]morphinan-6-one, 14 β -[(2-chlorobenzyl)oxy]-17-(cyclopropylmethyl)-4,5 α -epoxy-3-hydroxymorphinan-6-one, 14 β -benzyloxy-17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxymorphinan-6-one, 14 β -butoxy-17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxymorphinan-6-one, 17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-14 β -[(3-methylbutyl)oxy]morphinan-6-one, 4,5 α -epoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-3-[(prop-2-ynyl)oxy]morphinan-6-one, 14 β -[(3-chlorobenzyl)oxy]-4,5 α -epoxy-17-methyl-3-[(prop-2-ynyl)oxy]morphinan-6-one, 4,5 α -epoxy-17-ethyl-3-methoxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, 4,5 α -epoxy-17-ethyl-3-hydroxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, 4,5 α -epoxy-3-hydroxy-14 β -[(3-methylbutyl)oxy]-17-propylmorphinan-6-one, 5 β -benzyl-14-methoxycodeinone (= 5-benzyl-7,8-didehydro-4,5 α -epoxy-3,14 β -dimethoxy-17-methyl-morphinan-6-one), 5 β -benzyl-4,5 α -epoxy-3,14 β -dimethoxy-17-methylmorphinan-6-one, 5 β -benzyl-4,5 α -epoxy-3-hydroxy-14 β -methoxy-17-methylmorphinan-6-one, 4-hydroxy-3-methoxy-17-methyl-14-[(3-phenylpropyl)oxy]-morphinan-6-one, 3,4-dimethoxy-17-methyl-14-[(3-phenylpropyl)oxy]-morphinan-6-one, 14 β -benzyloxy-4-hydroxy-3-methoxy-17-methylmorphinan-6-one, 14 β -benzyloxy-3,4-dimethoxy-17-methylmorphinan-6-one, 4-hydroxy-3-methoxy-17-methyl-14 β -[(2-naphthylmethyl)oxy]morphinan-6-one, 3,4-dimethoxy-17-methyl-14 β -[(2-naphthylmethyl)oxy]morphinan-6-one, 4-hydroxy-3-methoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-morphinan-6-one, 3,4-dimethoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-morphinan-6-one, 14 β -ethoxy-4-hydroxy-3-methoxy-5 β ,17-dimethylmorphinan-6-one, 14 β -ethoxy-3,4-dimethoxy-5 β ,17-dimethylmorphinan-6-one, 14 β -benzyloxy-3,4-dimethoxy-5 β ,17-dimethylmorphinan-6-one, 4,5 α -epoxy-3-hydroxy-17,17-dimethyl-6-oxo-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, (17S)-4,5 α -epoxy-17-ethyl-3-hydroxy-17-methyl-6-oxo-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, (17R)-4,5 α -epoxy-3-hydroxy-17-methyl-6-oxo-14 β -[(3-phenylpropyl)oxy]-17-[(2(R,S)-tetrahydrofuran-2-yl)methyl]morphinan-6-one, (17R)-17-allyl-4,5 α -epoxy-14 β -ethoxy-3-hydroxy-17-methyl-6-oxomorphinan-6-one, (17R)-17-allyl-4,5 α -epoxy-3-hydroxy-14 β -methoxy-17-methyl-6-oxomorphinan-6-one, (17S)-17-allyl-4,5 α -epoxy-3-hydroxy-14 β -methoxy-17-methyl-6-oxomorphinan-6-one, 4,5 α -epoxy-3-hydroxy-14 β -methoxy-17,17-dimethyl-6-oxo-morphinan-6-one, 5 β -benzyl-14 β -(butoxy)-4,5-epoxy-3-hydroxy-17,17-dimethyl-6-oxomorphinan-6-one, (17S)-17-allyl-5 β -benzyl-14 β -butoxy-4,5 α -epoxy-3-hydroxy-17-methyl-6-oxomorphinan-6-one, 14 β -butoxy-4,5 α -epoxy-3-hydroxy-17,17-dimethyl-6-oxomorphinan-6-one, (17R)-17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-17-methyl-6-oxo-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, (17R)-17-cyclopropylmethyl-4,5 α -epoxy-3-methoxy-17-methyl-6-oxo-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, (17R)-17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-17-methyl-6-oxo-14 β -[(2-phenylbenzyl)oxy]morphinan-6-one, (17R)-14 β -[(4-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-17-methyl-6-oxomorphinan-6-one, (17R)-4,5 α -epoxy-3-hydroxy-14 β -methoxy-17-methyl-6-oxo-17-(2-phenylethyl)morphinan-6-one, 4,5 α -epoxy-3-methoxy-17-methyl-14 β -[(3-phenylpropyl)oxy]morphinan-6-one, 4,5 α -epoxy-3-methoxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,

4,5 α -epoxy-3-hydroxy-17-methyl-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 4,5 α -epoxy-17-methyl-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 17-(cyclopropylmethyl)-4,5 α -epoxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 4,5 α -epoxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 17-(cyclopropylmethyl)-4-hydroxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 17-(cyclopropylmethyl)-4-methoxy-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,
 4-(n-butyloxy)-17-(cyclopropylmethyl)-14 β -[(3-phenylpropyl)oxy]morphinan-6-one,

or any pharmaceutically acceptable salt or easily accessible derivative of it.

6. Composition, comprising a compound of Claims 1 to 5 and/or a pharmaceutically acceptable acid addition salt of it, together with a pharmaceutically acceptable carrier substance.
7. Compound according to any of Claims 1 to 6 as medicament.
8. Use of a compound of Claims 1 to 5 for the manufacture of a medicament for the treatment of pain, including chronic and acute pain, post-operative pain, rheumatic diseases (e.g. arthritis), ileus, obstipation, overweight, addiction, including opioid, cocaine and alcohol addiction as well as for the manufacture of a narcotic.
9. Compounds according to Claim 1 or 2, wherein X is oxygen.
10. Compounds according to Claim 1, 2 or 9, wherein R₅ is OH or alkoxy.
11. Compounds according to Claim 1, 2, 9 or 10, wherein R₃ is hydrogen, alkyl or aralkyl, preferably hydrogen or alkyl.
12. Compounds according to Claim 1, 2, 9, 10 or 11, wherein R₄ is OH, alkoxy or alkenyloxy or alkynyloxy.
13. Compounds according to Claim 1, 2, 9, 10, 11 or 12, wherein a single bond is present between the carbon atoms of the numbers 7 and 8.
14. Compounds according to Claim 1, 2, 9, 10, 11, 12 or 13, wherein R₂ is hydrogen, alkyl or aralkyl, preferably aralkyl.

15. Compounds according to Claim 1, 2, 9, 10, 11, 12, 13 or 14, wherein R₁ is alkyl, (cyclical saturated group)alkyl, aralkyl or alkenyl.

16. Compounds according to Claim 1 or 2, wherein R₁ is C₁-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkinyl; C₃-C₁₆-(cyclical saturated group)alkyl, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyl, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyl, where alkinyl is C₂-C₆; C₇-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyl, where aryl is C₆-C₁₀-aryl and alkinyl is C₂-C₆-alkinyl.

17. Compounds according to Claim 1, wherein R₂ is C₄-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkinyl; C₃-C₁₆-(cyclical saturated group)alkyl, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyl, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyl, where alkinyl is C₂-C₆; C₈-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyl, where aryl is C₆-C₁₀-aryl and alkinyl is C₂-C₆-alkinyl; C₃-C₆-alkenoyl; C₃-C₆-alkinoyl; C₉-C₁₆-arylalkenoyl, where aryl is C₆-C₁₀-aryl and alkenoyl is C₃-C₆-alkenoyl; C₉-C₁₆-arylalkinoyl, where aryl is C₆-C₁₀-aryl and alkinoyl is C₃-C₆-alkinoyl.

18. Compounds according to Claim 2, wherein R₂ is C₁-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkinyl; C₃-C₁₆-(cyclical saturated group)alkyl, where alkyl is C₁-C₆; C₄-C₁₆-(cyclical saturated group)alkenyl, where alkenyl is C₂-C₆; C₄-C₁₆-(cyclical saturated group)alkinyl, where alkinyl is C₂-C₆; C₆-C₁₆-arylalkyl, where aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl, where aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl; C₈-C₁₆-arylalkinyl, where aryl is C₆-C₁₀-aryl and alkinyl is C₂-C₆-alkinyl; C₃-C₆-alkenoyl; C₃-C₆-alkinoyl; C₉-C₁₆-arylalkenoyl, where aryl is C₆-C₁₀-aryl and alkenoyl is C₃-C₆-alkenoyl; C₉-C₁₆-arylalkinoyl, where aryl is C₆-C₁₀-aryl and alkinoyl is C₃-C₆-alkinoyl.

Morphinanderivate und deren quartäre Ammoniumsalze substituiert in Position 14, Herstellungsverfahren und Verwendung

Die vorliegende Erfindung betrifft eine Klasse von Morphinanverbindungen und deren quartäre Ammoniumsalze substituiert in Position 14, die als hochaktive Analgetika aber auch als Opioidantagonisten verwendet werden können. Die vorliegende Erfindung bezieht sich auch auf deren pharmazeutisch akzeptierbaren Salze und leicht zugänglichen Derivate, auf einen Prozess zu deren Herstellung und deren Verwendung in der Herstellung pharmazeutischer Spezialitäten.

Die Existenz von Opioid-Rezeptoren als Rezeptoren des Zentralnervensystems (ZNS), welche analgetische Wirkung vermitteln, ist eindeutig erwiesen. Diese Rezeptoren werden in drei Subtypen, μ , κ und δ eingeteilt. Aktivierung dieser Rezeptoren durch Opioidagonisten hat einen analgetischen Effekt zur Folge. Die Aktivierung der μ -Rezeptoren bewirkt den höchsten analgetischen Effekt, wobei besonders N-methylsubstituierte Morphinane mit einer Sauerstofffunktion in Position 6 (Morphin, Oxymorphon, Hydromorphon etc.) besonders aktive Opioidagonisten sind und als effektive Analgetika eingesetzt werden. In der Vergangenheit wurde viel Arbeit in Struktur-Aktivitäts-Beziehungsstudien dieser Substanzklasse investiert.

Im Journal of Medicinal Chemistry 1984, 27, S. 1575-1579 sind verschiedene 14-Methoxy-N-methylmorphinan-6-one mit verschiedenen Substituenten in Position 3 beschrieben. Diese Derivate zeigen höhere analgetische Aktivität als deren 14-Hydroxyanaloga.

Eine detaillierte Studie von 5-Methyloxymorphon (= 14-Hydroxy-5-methyldihydromorphinon) ist in Helvetica Chimica Acta (1988, 71, S. 1801-1804) beschrieben, die zu dem Ergebnis gelangt, daß die Einführung einer 5-Methylgruppe die opioidagonistischen Eigenschaften von Oxymorphon verringert.

Eine weitere Studie an 14-Alkoxy-N-methylmorphinan-6-onen ist in Helvetica Chimica Acta 1989, 72, S. 1233-1239 beschrieben, in welcher der Einfluß verschiedener Substituenten in Position 3 und des Aminstickstoffs evaluiert wurden.